REMARKS

Claims 81-83, 85, and 87-91 were pending in this application. Claims 84 and 86 were withdrawn from consideration as being directed to a non-elected invention. Claims 84, 85 and 86 are now cancelled without prejudice to Applicants' right to prosecute their subject matter in the present application and in related applications. Claims 83 and 87-91 are currently amended without any intent of disclaiming equivalents thereof. Accordingly, claims 81-83 and 87-91 are pending and presented for consideration.

Specification amendments

Applicants have amended the title to be indicative of the invention to which the pending claims are directed. In addition, Applicants have amended the specification to correct a hand-written notation and a typographical error. Support for the amendment is found in the specification at least, for example, at page 10, line 31, and at page 62, line 40. Applicants respectfully submit that the amendments to the specification introduce no new matter.

Claim amendments

Support for the amendment to claim 83 can be found in the specification as originally filed at least, for example, in the paragraph bridging pages 43 and 44, and in Figure 5 and accompanying text. Support for the amendment to claims 87-89 and 91 can be found in the specification as originally filed at least, for example, at page 60, the second paragraph. Claims 87, 88, 90 and 91 have also been amended to delete the reference to the cancelled claims and to correct informalities. Applicants respectfully submit that the amendments to the claims introduce no new matter.

Sequence Rules

The Office action objects to the application as being not fully in compliance with the sequence rules, 37 C.F.R. §§ 1.821-1.825. Specifically, the Office action alleges that the specification does not include sequence identifiers. Applicants submit that a Preliminary Amendment was filed on September 10, 2001, to introduce sequence identifiers into the specification. A copy of the Preliminary Amendment filed on September 10, 2001, is attached as

Exhibit A. Applicants respectfully request that the Preliminary Amendment of September 10, 2001, be entered and the objection be reconsidered and withdrawn.

Objection to the specification

The Office action objects to the specification for containing hand-written notations. The Office action also objects to the title of the invention for not being descriptive. Applicants have amended the specification and the title to overcome the objections. Accordingly, Applicants request reconsideration and withdrawal of the objection to the specification.

Claim objections

The Office action objects to claims 87-91 for depending from the non-elected inventions. Applicants have amended claims 87-91 to delete the reference to the non-elected inventions. Accordingly, Applicants request reconsideration and withdrawal of the objection to claims 87-91.

Claim Rejections Under 35 U.S.C. § 112, second paragraph

Claims 83, 85, 87-89 and 91 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Specifically, the Office action alleges that claim 83 fails to recite the method to determine the recited molecular weight. Claim 83 has been amended to recite "(a) a pair of unglycosylated polypeptide chains, each of said unglycosylated polypeptide chains having a molecular weight of about 14 kDa to 16 kDa, as determined by polyacrylamide gel electrophoresis under reducing conditions; or (b) an unglycosylated dimeric protein having a molecular weight of about 27 kDa, as determined by polyacrylamide gel electrophoresis under non-reducing conditions." In view of the amendment, Applicants request reconsideration and withdrawal of the rejection of claim 83.

The Office action alleges that the recitation "consisting essentially of" in claim 85 is not clear. Without acquiescing to the merits of the rejection and in order to speed prosecution of this application, Applicants have cancelled claim 85. In view of the cancellation of claim 85, Applicants request reconsideration and withdrawal of the rejection of claim 85.

The Office action alleges that claims 87-89 and 91 are not clear in terms of whether the claims are directed to isolated host cells or host cells in the context of multi-cellular transgenic organisms, possibly even humans. Applicants have amended the claims to recite "isolated host cell." Accordingly, Applicants request reconsideration and withdrawal of the rejection of claims 87-89 and 91.

Double Patenting

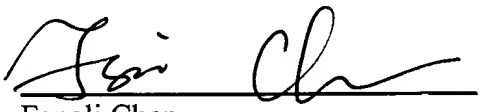
Applicants request that all double patenting rejections be held in abeyance until the presence of otherwise-allowable subject matter is acknowledged.

CONCLUSION

Claims 81-83 and 87-91 are presently pending in this application. The Examiner is invited to contact the undersigned with any questions about this paper. Early and favorable action is respectfully solicited.

Date: January 7, 2005
Reg. No. 51,551

Respectfully submitted,



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PATENT
Attorney Docket No. STK-008CN

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S):	Oppermann et al.		
SERIAL NO.:	09/754,831	GROUP NO.:	1647
FILING DATE:	January 3, 2001	EXAMINER:	
TITLE:	Osteogenic Devices		

Box Missing Parts
Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Applicants respectfully request entry of this Preliminary Amendment in the above-identified application. A Sequence Listing is submitted herewith in computer-readable form and paper form. A paper copy of the Sequence Listing is attached herewith for the Examiner's convenience. The claims and the specification are amended to insert sequence identifiers into the application. Applicants also respectfully request entry of the Sequence Listing in the above-identified application. No new matter is introduced.

The Sequence Listing and the present Preliminary Amendment are responsive to the Notice to File Missing Parts of Nonprovisional Application, mailed from the Patent Office on March 8, 2001.

Please make the following changes before examining the patent application identified above.

In the Claims

Please cancel claims 1-45, 50-80 without prejudice, and amend claims 46-49 to read as follows. A marked up version of the amended claims is attached at the end of this Preliminary Amendment.

46. (Amended) A DNA sequence encoding an amino acid sequence sufficiently duplicative of that of the sequence encoded by the gene of Figure 1A (SEQ ID NO: 40) such that said encoded sequence induces bone or cartilage formation when implanted in a mammal in association with a matrix.

47. (Amended) The DNA of claim 46 encoding the same amino acid sequence as the gene set forth in Figure 1A (SEQ ID NO: 40).

48. (Amended) The DNA sequence of claim 46 encoding:

```
     1        10          20          30          40
OP1        LYVSFR-DLGWQDWIIAPEGYAAYYCEGECAFPLNS
                 50          60          70
     YMNATN--H-AIVQTLVHFINPET-VPKPCCAPTQLNA
         80          90          100
     ISVLYFDDSSNVILKKYRNMVVRACGCH (SEQ ID NO: 39).
```

49. (Amended) The DNA sequence of the claim 46 encoding:

```
                                                -5
                                                HQRQA
     1        10          20          30          40
OP1  CKKHELYVSFR-DLGWQDWIIAPEGYAAYYCEGECAFPLNS
                 50          60          70
     YMNATN--H-AIVQTLVHFINPET-VPKPCCAPTQLNA
         80          90          100
     ISVLYFDDSSNVILKKYRNMVVRACGCH (SEQ ID NO: 9).
```

In the Specification:

Please amend the specification as follows to include sequence identifiers. A marked up version of the specification showing the amendments is attached at the end of this Preliminary Amendment.

Please replace the first full paragraph on page 8, line 1, with the following paragraph.

A series of consensus DNA sequences were designed with the goal of producing an active osteogenic protein. The sequences were based on partial amino acid sequence data obtained from the natural source product and on observed homologies with unrelated genes reported in the literature, or the sequences they encode, having a presumed or demonstrated developmental function. Several of the biosynthetic consensus sequences have been expressed as fusion proteins in procaryotes, purified, cleaved, refolded, combined with a matrix, implanted in an established animal model, and shown to have endochondral bone-inducing activity. The currently preferred active totally biosynthetic proteins comprise two synthetic sequences designated COP5 (SEQ ID NO: 1) and COP7 (SEQ ID NO: 2). The amino acid sequences of these proteins are set forth below.

Please replace the third paragraph starting on page 9, line 23, and ending on page 10, line 8, with the following paragraph.

In one preferred aspect, these proteins comprise species of the generic amino acid sequences (SEQ ID NO: 3 and SEQ ID NO: 4, respectively):

```
1         10         20         30         40         50
      LXVXFXDXGWXXWXXXPXGXXAXYCXGXCXXPXXXXXXXXXNHAXX
          60         70         80         90        100
QXXVXXXNXXXXPXXCCXPXXXXXXXXLXXXXXXXVXLXXYXXMXVXXCXCX

or
1         10         20         30         40         50
CXXXXLXVXFXDXGWXXWXXXPXGXXAXYCXGXCXXPXXXXXXXXXNHAXX
          60         70         80         90        100
QXXVXXXNXXXXPXXCCXPXXXXXXXXLXXXXXXXVXLXXYXXMXVXXCXCX
```

where the letters indicate the amino acid residues of standard single letter code, and the Xs represent amino acid residues. Preferred amino acid sequences within the foregoing generic sequences are (SEQ ID NO: 5 and SEQ ID NO: 6, respectively):

Please replace the second full paragraph on page 11, line 8, with the following paragraph.

Particular useful sequences include Vgl (SEQ ID NO: 7), DPP (SEQ ID NO: 8), OP1 (SEQ ID NO: 9), CBMP-2a (SEQ ID NO: 10), CBMP-2b (SEQ ID NO: 11), CBMP-3 (SEQ ID NO: 12), COP1 (SEQ ID NO: 13), COP3 (SEQ ID NO: 14), COP4 (SEQ ID NO: 15), and COP16 (SEQ ID NO: 16).

Please replace the second full paragraph on page 14, line 5, with the following paragraph.

Analysis of digestion fragments indicate that the native 30 kD osteogenic protein contains the following amino acid sequences (question marks indicate undetermined residues):

(1) S-F-D-A-Y-Y-C-S-G-A-C-Q-F-P-M-P-K (SEQ ID NO: 17);
(2) S-L-K-P-S-N-Y-A-T-I-Q-S-I-V (SEQ ID NO: 18);
(3) A-C-C-V-P-T-E-L-S-A-I-S-M-L-Y-L-D-E-N-E-K (SEQ ID NO: 19);
(4) M-S-S-L-S-I-L-F-F-D-E-N-K (SEQ ID NO: 20);
(5) S-Q-E-L-Y-V-D-F-Q-R (SEQ ID NO: 21);
(6) F-L-H-C-Q-F-S-E-R-N-S (SEQ ID NO: 22);
(7) T-V-G-Q-L-N-E-Q-S-S-E-P-N-I-Y (SEQ ID NO: 23);
(8) L-Y-D-P-M-V-V (SEQ ID NO: 24);
(9) V-G-V-V-P-G-I-P-E-P-C-C-V-P-E (SEQ ID NO: 25);
(10) V-D-F-A-D-I-G (SEQ ID NO: 26);
(11) V-P-K-P-C-C-A-P-T (SEQ ID NO: 27);
(12) I-N-I-A-N-Y-L (SEQ ID NO: 28);
(13) D-N-H-V-L-T-M-F-P-I-A-I-N (SEQ ID NO: 29);
(14) D-E-Q-T-L-K-K-A-R-R-K-Q-W-I-?-P (SEQ ID NO: 30);
(15) D-I-G-?-S-E-W-I-I-?-P (SEQ ID NO: 31);
(16) S-I-V-R-A-V-G-V-P-G-I-P-E-P-?-?-V (SEQ ID NO: 32);
(17) D-?-I-V-A-P-P-Q-Y-H-A-F-Y (SEQ ID NO: 33);
(18) D-E-N-K-N-V-V-L-K-V-Y-P-N-M-T-V-E (SEQ ID NO: 34);
(19) S-Q-T-L-Q-F-D-E-Q-T-L-K-?-A-R-?-K-Q (SEQ ID NO: 35);
(20) D-E-Q-T-L-K-K-A-R-R-K-Q-W-I-E-P-R-N-?-A-R-R-Y-L (SEQ ID NO: 36);
(21) A-R-R-K-Q-W-I-E-P-R-N-?-A-?-R-Y-?-?-V-D (SEQ ID NO: 37); and

(22) R-?-Q-W-I-E-P-?-N-?-A-?-?-Y-L-K-V-D-?-A-?-?-G (SEQ ID NO: 38).

Please replace the second full paragraph on page 16, line 5, with the following paragraph.

The consensus DNA sequences are also useful as probes for extracting genes encoding osteogenic protein from genomic and cDNA libraries. One of the consensus sequences has been used to isolate a heretofore unidentified genomic DNA sequence, portions of which when ligated encode a protein having a region capable of inducing endochondral bone formation. This protein, designated OP1, has an active region having the sequence set forth below (SEQ ID NO: 39 and SEQ ID NO: 9, respectively).

Please replace the fifth full paragraph on page 16, line 29, with the following paragraph.

Fig. 1A discloses the genomic DNA sequence of OP1 (SEQ ID NO: 40).

Please replace the second full paragraph on page 18, line 7, with the following paragraph.

FIGURE 1A represents the nucleotide sequence of the genomic copy of osteogenic protein "OP1" gene (SEQ ID NO: 40). The unknown region between 1880 and 1920 actually represents about 1000 nucleotides;

Please replace the third full paragraph on page 18, line 11, with the following paragraph.

FIGURE 1B is a representation of the hybridization of the consensus gene/probe (SEQ ID NO: 41) to the osteogenic protein "OP1" gene (SEQ ID NO: 42);

Please replace the third full paragraph on page 20, line 14, with the following paragraph.

FIGURE 13 is a schematic representation of the DNA sequence (SEQ ID NO: 43) and corresponding amino acid sequence (SEQ ID NO: 44) of a consensus gene/probe for osteogenic protein (COPO);

Please replace the second full paragraph on page 21, line 7, with the following paragraph.

FIGURE 18 is a comparison of the amino acid sequence of various osteogenic proteins to those of the TGF-beta family. COP1 (SEQ ID NO: 13), COP3 (SEQ ID NO: 14), COP4 (SEQ ID NO: 15), COP5 (SEQ ID NO: 1), and COP7 (SEQ ID NO: 2) are a family of analogs of synthetic osteogenic proteins developed from the consensus gene that was joined to a leader protein via a hinge region having the sequence D-P-N-G (SEQ ID NO: 45) that permitted chemical cleavage at the D-P site (by acid) or N-G (by hydroxylamine) resulting in the release of the analog protein; VGI (SEQ ID NO: 7) is a Xenopus protein, DPP (SEQ ID NO: 8) is a Drosophila protein; OP1 (amino acids 6-x of SEQ ID NO: 9) is a native osteogenic protein; CBMP2a (SEQ ID NO: 10) and 2b (SEQ ID NO: 11), and CBMP3 (SEQ ID NO: 12) are subparts of proteins disclosed in PCT application 087/01537; beta-Inhibin a) is shown in SEQ ID NO: 46, beta-Inhibin b) is shown in SEQ ID NO: 47, TGF-beta 1 is shown in SEQ ID NO: 48, TGF-beta 2 is shown in SEQ ID NO: 49, TGF-beta 3 is shown in SEQ ID NO: 50; MIS (SEQ ID NO: 51) is Mullerian inhibitory substance; alpha-Inhibin is shown in SEQ ID NO: 52; and "consensus choices" represent various substitutions of amino acids that may be made at various positions in osteogenic proteins;

Please replace the second full paragraph on page 22, line 4, with the following paragraph.

FIGURE 21B is the DNA sequence (SEQ ID NO: 53) and amino acid sequence (SEQ ID NO: 54) comprising a modified trp-LE leader, two Fb domains of protein A, an ASP-PRO cleavage site, and the COP5 sequence;

Please replace the second paragraph starting on page 47, line 9, and ending on page 48, line 4, with the following paragraph.

Various of the peptide fragments produced using the foregoing procedures have been analyzed in an automated amino acid sequencer (Applied Biosystems 470A with 120A on-line PTH analysis). The following sequence data has been obtained:

(1) S-F-D-A-Y-Y-C-S-G-A-C-Q-F-P-M-P-K (SEQ ID NO: 17);
(2) S-L-K-P-S-N-Y-A-T-I-Q-S-I-V (SEQ ID NO: 18);

(3) A-C-C-V-P-T-E-L-S-A-I-S-M-L-Y-L-D-E-N-E-K (SEQ ID NO: 19);
(4) M-S-S-L-S-I-L-F-F-D-E-N-K (SEQ ID NO: 20);
(5) S-Q-E-L-Y-V-D-F-Q-R (SEQ ID NO: 21);
(6) F-L-H-C-Q-F-S-E-R-N-S (SEQ ID NO: 22);
(7) T-V-G-Q-L-N-E-Q-S-S-E-P-N-I-Y (SEQ ID NO: 23);
(8) L-Y-D-P-M-V-V (SEQ ID NO: 24);
(9) V-G-V-V-P-G-I-P-E-P-C-C-V-P-E (SEQ ID NO: 25);
(10) V-D-F-A-D-I-G (SEQ ID NO: 26);
(11) V-P-K-P-C-C-A-P-T (SEQ ID NO: 27);
(12) I-N-I-A-N-Y-L (SEQ ID NO: 28);
(13) D-N-H-V-L-T-M-F-P-I-A-I-N (SEQ ID NO: 29);
(14) D-E-Q-T-L-K-K-A-R-R-K-Q-W-I-?-P (SEQ ID NO: 30);
(15) D-I-G-?-S-E-W-I-I-?-P (SEQ ID NO: 31);
(16) S-I-V-R-A-V-G-V-P-G-I-P-E-P-?-?-V (SEQ ID NO: 32);
(17) D-?-I-V-A-P-P-Q-Y-H-A-F-Y (SEQ ID NO: 33);
(18) D-E-N-K-N-V-V-L-K-V-Y-P-N-M-T-V-E (SEQ ID NO: 34);
(19) S-Q-T-L-Q-F-D-E-Q-T-L-K-?-A-R-?-K-Q (SEQ ID NO: 35);
(20) D-E-Q-T-L-K-K-A-R-R-K-Q-W-I-E-P-R-N-?-A-R-R-Y-L (SEQ ID NO: 36);
(21) A-R-R-K-Q-W-I-E-P-R-N-?-A-?-R-Y-?-?-V-D (SEQ ID NO: 37); and
(22) R-?-Q-W-I-E-P-?-N-?-A-?-?-Y-L-K-V-D-?-A-?-?-G (SEQ ID NO: 38).

Please replace Table 6 page 54-55, with the following Table 6.

TABLE 6

protein	amino acid sequence	homology
(BOP) SEQ ID NO: 55	SFDAYYCSGACQFPS ***** * * **	(9/15 matches)
(DDP) SEQ ID NO: 56	GYDAYYCHGKCPFFL	
(BOP) SEQ ID NO: 55	SFDAYYCSGACQFPS * ** * * *	(6/15 matches)
(Vg1) SEQ ID NO: 57	GYMANYCYGECPYPL	
(BOP) SEQ ID NO: 55	SFDAYYCSGACQFPS * ** * *	(5/15 matches)
(inhibin) SEQ ID NO: 58	GYHANYCEGECPSHI	

(BOP) SEQ ID NO: 55	SFDAYYCSGACQFPS	(4/15 matches)
	* * * *	
(TGF-beta) SEQ ID NO: 59	GYHANFCLGPCPYIW	

(BOP) SEQ ID NO: 60	K/RACCVPTELSAISMLYLDEN	(12/20 matches)
	***** * **** * *	
(Vgl) SEQ ID NO: 61	LPCCVPTKMSPISMLFYDNN	

(BOP) SEQ ID NO: 60	K/RACCVPTELSAISMLYLDEN	(12/20 matches)
	* ***** * **** *	
(inhibin) SEQ ID NO: 62	KSCCVPTKLRPMSMLYYDDG	

(BOP) SEQ ID NO: 60	K/RACCVPTELSAISMLYLDE	(6/19 matches)
	**** * *	
(TGF-beta) SEQ ID NO: 63	APCCVPQALEPLPIVYYVG	

(BOP) SEQ ID NO: 60	K/RACCVPTELSAISMLYLDEN	(12/20 matches)
	******* * ****	
(DPP) SEQ ID NO: 64	KACCVPTQLDSVAMLYLNDQ	

(BOP) SEQ ID NO: 65	LYVDF	(5/5 matches)
	*****	
(DPP) SEQ ID NO: 66	LYVDF	

(BOP) SEQ ID NO: 65	LYVDF	(4/5 matches)
	*** *	
(Vgl) SEQ ID NO: 67	LYVEF	

(BOP) SEQ ID NO: 65	LYVDF	(4/5 matches)
	** **	
(TGF-beta) SEQ ID NO: 68	LYIDF	

(BOP) SEQ ID NO: 65	LYVDF	(2/4 matches)
	* *	
(inhibin) SEQ ID NO: 69	FFVSF	

-
*-match

Please replace the second paragraph starting on page 57, line 14, and ending on page 58, line 27, with the following paragraph.

Southern blot analysis of lambda #13 DNA showed that an approximately 3kb BamHI fragment hybridized to the probe. (See Fig. 1B). This fragment was isolated and subcloned into a bluescript vector (at the BamHI site). The clone was further analyzed by Southern blotting and hybridization to the COP0 probe. This showed that a 1kb (approx.) EcoRI fragment strongly hybridized to the probe. This fragment was subcloned into the EcoRI site of a bluescript vector, and sequenced. Analysis of this sequence showed that the fragment encoded the carboxy terminus of a protein, named osteogenic protein-1 (OP1). The protein was identified by amino acid homology with the TGF-beta family. For this comparison cysteine patterns were used and then the adjacent amino acids were compared. Consensus splice signals were found where amino acid homologies ended, designating exon intron boundaries. Three exons were combined to obtain a functional TGF-beta-like domain containing seven cysteines. Two introns were deleted by looping out via primers bridging the exons using the single stranded mutagensis method of Kunkel. Also, upstream of the first cysteine, an EcoRI site and an asp-pro junction for acid cleavage were introduced, and at the 3' end a PstI site was added by the same technique. Further sequence information (penultimate exon) was obtained by sequencing the entire insert. The sequencing was done by generating a set of unidirectionally deleted clones (Ozkaynak, E., and Putney, S.: Biotechniques, 5, 770-773, 1987). The obtained sequence covers about 80% of the TGF-beta-like region of OP1 and is set forth in FIG. 1A (SEQ ID NO: 40). The complete sequence of the TGF-beta like region was obtained by first subcloning all EcoRI generated fragments of lambda clone #13 DNA and sequencing a 4kb fragment that includes the first portion of the TGF-beta like region (third exon counting from end) as well as sequences characterized earlier. The gene on an EcoRI to PstI fragment was inserted into an E. coli expression vector controlled by the trp promoter-operator to produce a modified trp LE fusion protein with an acid cleavage site. The OP1 gene encodes amino acids corresponding substantially to a peptide found in sequences of naturally sourced material. The amino acid sequence of what is believed to be its active region is set forth below (SEQ ID NO: 39):

Please replace the first full paragraph on page 59, line 1, with the following paragraph.

A longer active sequence is (SEQ ID NO: 9):

Please replace the third paragraph starting on page 61, line 27, and ending on page 62, line 28, with the following paragraph.

It was noted, for example, that DPP from drosophila, VG1 from Xenopus, the TGF beta family of proteins, and to a lesser extent, alpha and beta inhibins, had significant homologies with certain of the sequences derived from the naturally sourced OP product. (Fig. 18.) Study of these proteins led to the realization that a portion of the sequence of each had a structural similarity observable by analysis of the positional relationship of cysteines and other amino acids which have an important influence on three dimensional protein conformation. It was noted that a region of these sequences had a series of seven cysteines, placed very nearly in the same relative positions, and certain other amino acids in sequence as set forth below (SEQ ID NO: 4):

```
         10          20          30          40          50
CXXXXLXVXFXDXGWXXWXXXPXGXXAXYCXGXCXXPXXXXXXXXNHAXX
         60          70          80          90         100
QXXVXXXNXXXXPXXCCXPXXXXXXXXLXXXXXXXVXLXXYXXMXVXXCXCX
```

wherein each X independently represents an amino acid. Expression experiments with constructs patterned after this template amino acid sequence showed activity occurred with a shorter sequence having only six cysteines (SEQ ID NO: 3):

```
         10          20          30          40          50
      LXVXFXDXGWXXWXXXPXGXXAXYCXGXCXXPXXXXXXXXNHAXX
         60          70          80          90         100
QXXVXXXNXXXXPXXCCXPXXXXXXXXLXXXXXXXVXLXXYXXMXVXXCXCX
```

wherein each X independently represents an amino acid. Within these generic structures are a multiplicity of specific sequences which have osteogenic or chondrogenic activity. Preferred structures are those having the amino acid sequence (SEQ ID NO: 6):

```
         10          20          30          40          50
CKRHPLYVDFRDVGWNDWIVAPPGYHAFYCHGECPFPLADHLNSTNHAIV
```

```
RRRS K S S L  QE VIS E FD Y  E A AY MPESMKAS   VI
  KE F E K I  DN     L    N  S   Q  ITK F P    TL
   Q     A    S      K

        60         70         80         90        100
QTLVNSVNPGKIPKACCVPTELSAISMLYLDENENVVLKNYQDMVVEGCGCR
 SI HAI SEQV EP  A EQMNSLAI FFNDQDK I RK EE T DA H H
    RF    T   S     K DPV V  Y N S     H RN   RS
     N    S                        K       P     E
```

wherein, in each position where more than one amino acid is shown, any one of the amino acids shown may be used. Novel active proteins also are defined by amino acid sequences comprising an active domain beginning at residue number 6 of this sequence, i.e., omitting the N terminal CXXXX, or omitting any of the preferred specific combinations such as CKRHP (SEQ ID NO: 70), CRRKQ (SEQ ID NO: 71), CKRHE (SEQ ID NO: 72), etc, resulting in a construct having only 6 cysteine residues. After this work, PCT 87/01537 was published, and it was observed that the proteins there identified as BMPII a and b and BMPIII each comprised a region embodying this generic structure. These proteins were not demonstrated to be osteogenic in the published application. However, applicants discovered that a subpart of the amino acid sequence of these protein, properly folded, and implanted as set forth herein, is active. These are disclosed herein as CBMPIIa, CBMPIIb, and CMBPIII. Also, the OP1 protein was observed to exhibit the same generic structure.

Please replace the first full paragraph on page 63, line 21, with the following paragraph.

Thus, the preferred osteogenic proteins are expressed from recombinant DNA and comprise amino acid sequences including any of the following sequences Vgl (SEQ ID NO: 7), DPP (SEQ ID NO: 8), OP1 (SEQ ID NO: 39), OP1 (SEQ ID NO: 9), CBMP-2a (SEQ ID NO: 10), CBMP-2b (SEQ ID NO: 11), CBMP-3 (SEQ ID NO: 12), COP1 (SEQ ID NO: 13), COP3 (SEQ ID NO: 14), COP4 (SEQ ID NO: 15), COP5 (SEQ ID NO: 1), COP7 (SEQ ID NO:2), and COP16 (SEQ ID NO: 16):

Please replace the sixth full paragraph on page 65, line 33, with the following paragraph.

As shown in FIGURE 18, these sequences have considerable homology with the alpha and beta inhibins (SEQ ID NOS: 52, 46 and 47, respectively), three forms of TGF beta (SEQ ID NOS: 48, 49, and 50, respectively), and MIS (SEQ ID NO: 51).

REMARKS

Claims 1-45 and 50-80 are canceled without prejudice and without any intention to abandon the subject matter claimed therein. Indeed, Applicants may still pursue claims of equal, lesser or greater scope. No new matter has been added by this amendment.

Claims 46-49 and the specification are amended to introduce sequence identifiers. Applicants respectfully submit that no new matter is introduced with this amendment.

A marked up version of the amended claims and a marked up version of the replacement paragraphs showing amendments are attached. A petition and fee for a four month extension of time up to and including September 10, 2001, is submitted herewith (September 8, 2001 was a Saturday). In the event that any additional fees are due, the Commissioner is hereby authorized to charge any such fees to Attorney's Deposit Account No. 20-0531.

Applicants respectfully submit that all of the pending claims are in condition for allowance and request early favorable action. If, in the Examiner's opinion, a telephonic interview would expedite allowance of the claims, the undersigned agent invites the Examiner to call him at the telephone number given below.

Respectfully submitted,

Date: September 10, 2001
Reg. No. 41,418

Patrick R. H. Waller, Ph.D.
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Testa, Hurwitz, & Thibeault, LLP
High Street Tower
125 High Street
Boston, Massachusetts 02110

Tel. No.: (617) 248-7240
Fax No.: (617) 248-7100

MARKED-UP VERSION OF SPECIFICATION SHOWING AMENDMENTS

Replacement paragraph for the first full paragraph on page 8, line 1.

A series of consensus DNA sequences were designed with the goal of producing an active osteogenic protein. The sequences were based on partial amino acid sequence data obtained from the natural source product and on observed homologies with unrelated genes reported in the literature, or the sequences they encode, having a presumed or demonstrated developmental function. Several of the biosynthetic consensus sequences have been expressed as fusion proteins in procaryotes, purified, cleaved, refolded, combined with a matrix, implanted in an established animal model, and shown to have endochondral bone-inducing activity. The currently preferred active totally biosynthetic proteins comprise two synthetic sequences designated COP5 (SEQ ID NO: 1) and COP7 (SEQ ID NO: 2). The amino acid sequences of these proteins are set forth below.

Replacement paragraph for the third paragraph starting on page 9, line 23, and ending on page 10, line 8.

In one preferred aspect, these proteins comprise species of the generic amino acid sequences (SEQ ID NO: 3 and SEQ ID NO: 4, respectively):

```
1         10         20         30         40         50
      LXVXFXDXGWXXWXXXPXGXXAXYCXGXCXXPXXXXXXXXXNHAXX
          60         70         80         90        100
QXXVXXXNXXXXPXXCCXPXXXXXXXXLXXXXXXXVXLXXYXXMXVXXCXCX

or
1         10         20         30         40         50
CXXXXLXVXFXDXGWXXWXXXPXGXXAXYCXGXCXXPXXXXXXXXXNHAXX
          60         70         80         90        100
QXXVXXXNXXXXPXXCCXPXXXXXXXXLXXXXXXXVXLXXYXXMXVXXCXCX
```

where the letters indicate the amino acid residues of standard single letter code, and the Xs represent amino acid residues. Preferred amino acid sequences within the foregoing generic sequences are (SEQ ID NO: 5 and SEQ ID NO: 6, respectively):

Replacement paragraph for the second full paragraph on page 11, line 8.

Particular useful sequences include Vgl (SEQ ID NO: 7), DPP (SEQ ID NO: 8), OP1 (SEQ ID NO: 9), CBMP-2a (SEQ ID NO: 10), CBMP-2b (SEQ ID NO: 11), CBMP-3 (SEQ ID NO: 12), COP1 (SEQ ID NO: 13), COP3 (SEQ ID NO: 14), COP4 (SEQ ID NO: 15), and COP16 (SEQ ID NO: 16):

Replacement paragraph for the second full paragraph on page 14, line 5.

Analysis of digestion fragments indicate that the native 30 kD osteogenic protein contains the following amino acid sequences (question marks indicate undetermined residues):

(1) S-F-D-A-Y-Y-C-S-G-A-C-Q-F-P-M-P-K (SEQ ID NO: 17);
(2) S-L-K-P-S-N-Y-A-T-I-Q-S-I-V (SEQ ID NO: 18);
(3) A-C-C-V-P-T-E-L-S-A-I-S-M-L-Y-L-D-E-N-E-K (SEQ ID NO: 19);
(4) M-S-S-L-S-I-L-F-F-D-E-N-K (SEQ ID NO: 20);
(5) S-Q-E-L-Y-V-D-F-Q-R (SEQ ID NO: 21);
(6) F-L-H-C-Q-F-S-E-R-N-S (SEQ ID NO: 22);
(7) T-V-G-Q-L-N-E-Q-S-S-E-P-N-I-Y (SEQ ID NO: 23);
(8) L-Y-D-P-M-V-V (SEQ ID NO: 24);
(9) V-G-V-V-P-G-I-P-E-P-C-C-V-P-E (SEQ ID NO: 25);
(10) V-D-F-A-D-I-G (SEQ ID NO: 26);
(11) V-P-K-P-C-C-A-P-T (SEQ ID NO: 27);
(12) I-N-I-A-N-Y-L (SEQ ID NO: 28);
(13) D-N-H-V-L-T-M-F-P-I-A-I-N (SEQ ID NO: 29);
(14) D-E-Q-T-L-K-K-A-R-R-K-Q-W-I-?-P (SEQ ID NO: 30);
(15) D-I-G-?-S-E-W-I-I-?-P (SEQ ID NO: 31);
(16) S-I-V-R-A-V-G-V-P-G-I-P-E-P-?-?-V (SEQ ID NO: 32);
(17) D-?-I-V-A-P-P-Q-Y-H-A-F-Y (SEQ ID NO: 33);
(18) D-E-N-K-N-V-V-L-K-V-Y-P-N-M-T-V-E (SEQ ID NO: 34);
(19) S-Q-T-L-Q-F-D-E-Q-T-L-K-?-A-R-?-K-Q (SEQ ID NO: 35);
(20) D-E-Q-T-L-K-K-A-R-R-K-Q-W-I-E-P-R-N-?-A-R-R-Y-L (SEQ ID NO: 36);
(21) A-R-R-K-Q-W-I-E-P-R-N-?-A-?-R-Y-?-?-V-D (SEQ ID NO: 37); and
(22) R-?-Q-W-I-E-P-?-N-?-A-?-?-Y-L-K-V-D-?-A-?-?-G (SEQ ID NO: 38).

Replacement paragraph for the second full paragraph on page 16, line 5.

The consensus DNA sequences are also useful as probes for extracting genes encoding osteogenic protein from genomic and cDNA libraries. One of the consensus sequences has been used to isolate a heretofore unidentified genomic DNA sequence, portions of which when ligated encode a protein having a region capable of inducing endochondral bone formation. This protein, designated OP1, has an active region having the sequence set forth below (SEQ ID NO: 39 and SEQ ID NO: 9, respectively).

Replacement paragraph for the fifth full paragraph on page 16, line 29.

Fig. 1A discloses the genomic DNA sequence of OP1 (SEQ ID NO: 40).

Replacement paragraph for the second full paragraph on page 18, line 7.

FIGURE 1A represents the nucleotide sequence of the genomic copy of osteogenic protein "OP1" gene (SEQ ID NO: 40). The unknown region between 1880 and 1920 actually represents about 1000 nucleotides;

Replacement paragraph for the third full paragraph on page 18, line 11.

FIGURE 1B is a representation of the hybridization of the consensus gene/probe (SEQ ID NO: 41) to the osteogenic protein "OP1" gene (SEQ ID NO: 42);

Replacement paragraph for the third full paragraph on page 20, line 14.

FIGURE 13 is a schematic representation of the DNA sequence (SEQ ID NO: 43) and corresponding amino acid sequence (SEQ ID NO: 44) of a consensus gene/probe for osteogenic protein (COPO);

Replacement paragraph for the second full paragraph on page 21, line 7.

FIGURE 18 is a comparison of the amino acid sequence of various osteogenic proteins to those of the TGF-beta family. COP1 (SEQ ID NO: 13), COP3 (SEQ ID NO: 14), COP4 (SEQ ID NO: 15), COP5 (SEQ ID NO: 1), and COP7 (SEQ ID NO: 2) are a family of analogs of

synthetic osteogenic proteins developed from the consensus gene that was joined to a leader protein via a hinge region having the sequence D-P-N-G (SEQ ID NO: 45) that permitted chemical cleavage at the D-P site (by acid) or N-G (by hydroxylamine) resulting in the release of the analog protein; VGI (SEQ ID NO: 7) is a Xenopus protein, DPP (SEQ ID NO: 8) is a Drosophila protein; OP1 (amino acids 6-x of SEQ ID NO: 9) is a native osteogenic protein; CBMP2a (SEQ ID NO: 10) and 2b (SEQ ID NO: 11), and CBMP3 (SEQ ID NO: 12) are subparts of proteins disclosed in PCT application 087/01537; beta-Inhibin a) is shown in SEQ ID NO: 46, beta-Inhibin b) is shown in SEQ ID NO: 47, TGF-beta 1 is shown in SEQ ID NO: 48, TGF-beta 2 is shown in SEQ ID NO: 49, TGF-beta 3 is shown in SEQ ID NO: 50; MIS (SEQ ID NO: 51) is Mullerian inhibitory substance; alpha-Inhibin is shown in SEQ ID NO: 52; and "consensus choices" represent various substitutions of amino acids that may be made at various positions in osteogenic proteins;

Replacement paragraph for the second full paragraph on page 22, line 4.

FIGURE 21B is the DNA sequence (SEQ ID NO: 53) and amino acid sequence (SEQ ID NO: 54) comprising a modified trp-LE leader, two Fb domains of protein A, an ASP-PRO cleavage site, and the COP5 sequence;

Replacement paragraph for the second paragraph starting on page 47, line 9, and ending on page 48, line 4.

Various of the peptide fragments produced using the foregoing procedures have been analyzed in an automated amino acid sequencer (Applied Biosystems 470A with 120A on-line PTH analysis). The following sequence data has been obtained:

(1) S-F-D-A-Y-Y-C-S-G-A-C-Q-F-P-M-P-K (SEQ ID NO: 17);
(2) S-L-K-P-S-N-Y-A-T-I-Q-S-I-V (SEQ ID NO: 18);
(3) A-C-C-V-P-T-E-L-S-A-I-S-M-L-Y-L-D-E-N-E-K (SEQ ID NO: 19);
(4) M-S-S-L-S-I-L-F-F-D-E-N-K (SEQ ID NO: 20);
(5) S-Q-E-L-Y-V-D-F-Q-R (SEQ ID NO: 21);
(6) F-L-H-C-Q-F-S-E-R-N-S (SEQ ID NO: 22);
(7) T-V-G-Q-L-N-E-Q-S-S-E-P-N-I-Y (SEQ ID NO: 23);
(8) L-Y-D-P-M-V-V (SEQ ID NO: 24);
(9) V-G-V-V-P-G-I-P-E-P-C-C-V-P-E (SEQ ID NO: 25);

(10) V-D-F-A-D-I-G (SEQ ID NO: 26);
(11) V-P-K-P-C-C-A-P-T (SEQ ID NO: 27);
(12) I-N-I-A-N-Y-L (SEQ ID NO: 28);
(13) D-N-H-V-L-T-M-F-P-I-A-I-N (SEQ ID NO: 29);
(14) D-E-Q-T-L-K-K-A-R-R-K-Q-W-I-?-P (SEQ ID NO: 30);
(15) D-I-G-?-S-E-W-I-I-?-P (SEQ ID NO: 31);
(16) S-I-V-R-A-V-G-V-P-G-I-P-E-P-?-?-V (SEQ ID NO: 32);
(17) D-?-I-V-A-P-P-Q-Y-H-A-F-Y (SEQ ID NO: 33);
(18) D-E-N-K-N-V-V-L-K-V-Y-P-N-M-T-V-E (SEQ ID NO: 34);
(19) S-Q-T-L-Q-F-D-E-Q-T-L-K-?-A-R-?-K-Q (SEQ ID NO: 35);
(20) D-E-Q-T-L-K-K-A-R-R-K-Q-W-I-E-P-R-N-?-A-R-R-Y-L (SEQ ID NO: 36);
(21) A-R-R-K-Q-W-I-E-P-R-N-?-A-?-R-Y-?-?-V-D (SEQ ID NO: 37); and
(22) R-?-Q-W-I-E-P-?-N-?-A-?-?-Y-L-K-V-D-?-A-?-?-G (SEQ ID NO: 38).

Replacement Table 6 on pages 54 and 55.

TABLE 6

protein	amino acid sequence	homology
(BOP) SEQ ID NO: 55 (DDP) SEQ ID NO: 56	SFDAYYCSGACQFPS ***** * * ** GYDAYYCHGKCPFFL	(9/15 matches)
(BOP) SEQ ID NO: 55 (Vgl) SEQ ID NO: 57	SFDAYYCSGACQFPS * ** * * * GYMANYCYGECPYPL	(6/15 matches)
(BOP) SEQ ID NO: 55 (inhibin) SEQ ID NO: 58	SFDAYYCSGACQFPS * ** * * GYHANYCEGECPSHI	(5/15 matches)
(BOP) SEQ ID NO: 55 (TGF-beta) SEQ ID NO: 59	SFDAYYCSGACQFPS * * * * GYHANFCLGPCPYIW	(4/15 matches)
(BOP) SEQ ID NO: 60 (Vgl) SEQ ID NO: 61	K/RACCVPTELSAISMLYLDEN ***** * **** * * LPCCVPTKMSPISMLFYDNN	(12/20 matches)

(BOP) SEQ ID NO: 60	K/RACCVPTELSAISMLYLDEN	(12/20 matches)
	* ***** * **** *	
(inhibin) SEQ ID NO: 62	KSCCVPTKLRPMSMLYYDDG	
(BOP) SEQ ID NO: 60	K/RACCVPTELSAISMLYLDE	(6/19 matches)
	**** * *	
(TGF-beta) SEQ ID NO: 63	APCCVPQALEPLPIVYYVG	
(BOP) SEQ ID NO: 60	K/RACCVPTELSAISMLYLDEN	(12/20 matches)
	******* * ****	
(DPP) SEQ ID NO: 64	KACCVPTQLDSVAMLYLNDQ	
(BOP) SEQ ID NO: 65	LYVDF	(5/5 matches)
	*****	
(DPP) SEQ ID NO: 66	LYVDF	
(BOP) SEQ ID NO: 65	LYVDF	(4/5 matches)
	*** *	
(Vgl) SEQ ID NO: 67	LYVEF	
(BOP) SEQ ID NO: 65	LYVDF	(4/5 matches)
	** **	
(TGF-beta) SEQ ID NO: 68	LYIDF	
(BOP) SEQ ID NO: 65	LYVDF	(2/4 matches)
	* *	
(inhibin) SEQ ID NO: 69	FFVSF	

-
*-match

Replacement paragraph for the second paragraph starting on page 57, line 14, and ending on page 58, line 27.

Southern blot analysis of lambda #13 DNA showed that an approximately 3kb BamHI fragment hybridized to the probe. (See Fig. 1B). This fragment was isolated and subcloned into a bluescript vector (at the BamHI site). The clone was further analyzed by Southern blotting and hybridization to the COP0 probe. This showed that a 1kb (approx.) EcoRI fragment strongly hybridized to the probe. This fragment was subcloned into the EcoRI site of a bluescript vector,

and sequenced. Analysis of this sequence showed that the fragment encoded the carboxy terminus of a protein, named osteogenic protein-1 (OP1). The protein was identified by amino acid homology with the TGF-beta family. For this comparison cysteine patterns were used and then the adjacent amino acids were compared. Consensus splice signals were found where amino acid homologies ended, designating exon intron boundaries. Three exons were combined to obtain a functional TGF-beta-like domain containing seven cysteines. Two introns were deleted by looping out via primers bridging the exons using the single stranded mutagensis method of Kunkel. Also, upstream of the first cysteine, an EcoRI site and an asp-pro junction for acid cleavage were introduced, and at the 3' end a PstI site was added by the same technique. Further sequence information (penultimate exon) was obtained by sequencing the entire insert. The sequencing was done by generating a set of unidirectionally deleted clones (Ozkaynak, E., and Putney, S.: Biotechniques, 5, 770-773, 1987). The obtained sequence covers about 80% of the TGF-beta-like region of OP1 and is set forth in FIG. 1A (SEQ ID NO: 40). The complete sequence of the TGF-beta like region was obtained by first subcloning all EcoRI generated fragments of lambda clone #13 DNA and sequencing a 4kb fragment that includes the first portion of the TGF-beta like region (third exon counting from end) as well as sequences characterized earlier. The gene on an EcoRI to PstI fragment was inserted into an E. coli expression vector controlled by the trp promoter-operator to produce a modified trp LE fusion protein with an acid cleavage site. The OP1 gene encodes amino acids corresponding substantially to a peptide found in sequences of naturally sourced material. The amino acid sequence of what is believed to be its active region is set forth below (SEQ ID NO: 39):

Replacement paragraph for the first full paragraph on page 59, line 1.

A longer active sequence is (SEQ ID NO: 9):

Replacement paragraph for the third paragraph starting on page 61, line 27, and ending on page 62, line 28.

It was noted, for example, that DPP from drosophila, VG1 from Xenopus, the TGF beta family of proteins, and to a lesser extent, alpha and beta inhibins, had significant homologies with certain of the sequences derived from the naturally sourced OP product. (Fig. 18.) Study of

these proteins led to the realization that a portion of the sequence of each had a structural similarity observable by analysis of the positional relationship of cysteines and other amino acids which have an important influence on three dimensional protein conformation. It was noted that a region of these sequences had a series of seven cysteines, placed very nearly in the same relative positions, and certain other amino acids in sequence as set forth below (SEQ ID NO: 4):

```
         10          20          30          40          50
CXXXXLXVXFXDXGWXXWXXXPXGXXAXYCXGXCXXPXXXXXXXXNHAXX
         60          70          80          90         100
QXXVXXXNXXXXPXXCCXPXXXXXXXXLXXXXXXXVXLXXYXXMXVXXCXCX
```

wherein each X independently represents an amino acid. Expression experiments with constructs patterned after this template amino acid sequence showed activity occurred with a shorter sequence having only six cysteines (SEQ ID NO: 3):

```
         10          20          30          40          50
      LXVXFXDXGWXXWXXXPXGXXAXYCXGXCXXPXXXXXXXXNHAXX
         60          70          80          90         100
QXXVXXXNXXXXPXXCCXPXXXXXXXXLXXXXXXXVXLXXYXXMXVXXCXCX
```

wherein each X independently represents an amino acid. Within these generic structures are a multiplicity of specific sequences which have osteogenic or chondrogenic activity. Preferred structures are those having the amino acid sequence (SEQ ID NO: 6):

```
         10          20          30          40          50
CKRHPLYVDFRDVGWNDWIVAPPGYHAFYCHGECPFPLADHLNSTNHAIV
 RRRS K S S L  QE VIS E FD Y  E A AY MPESMKAS   VI
   KE F E K I  DN     L    N  S   Q  ITK F P    TL
    Q     A    S      K

         60          70          80          90         100
QTLVNSVNPGKIPKACCVPTELSAISMLYLDENENVVLKNYQDMVVEGCGCR
 SI HAI SEQV EP  A EQMNSLAI FFNDQDK I RK EE T DA H H
    RF    T   S     K DPV V  Y N S     H RN   RS
     N    S                    K       P     E
```

wherein, in each position where more than one amino acid is shown, any one of the amino acids shown may be used. Novel active proteins also are defined by amino acid sequences comprising an active domain beginning at residue number 6 of this sequence, i.e., omitting the N terminal

CXXXX, or omitting any of the preferred specific combinations such as CKRHP (SEQ ID NO: 70), CRRKQ (SEQ ID NO: 71), CKRHE (SEQ ID NO: 72), etc, resulting in a construct having only 6 cysteine residues. After this work, PCT 87/01537 was published, and it was observed that the proteins there identified as BMPII a and b and BMPIII each comprised a region embodying this generic structure. These proteins were not demonstrated to be osteogenic in the published application. However, applicants discovered that a subpart of the amino acid sequence of these protein, properly folded, and implanted as set forth herein, is active. These are disclosed herein as CBMPIIa, CBMPIIb, and CMBPIII. Also, the OP1 protein was observed to exhibit the same generic structure.

Replacement paragraph for the first full paragraph on page 63, line 21.

Thus, the preferred osteogenic proteins are expressed from recombinant DNA and comprise amino acid sequences including any of the following sequences Vgl (SEQ ID NO: 7), DPP (SEQ ID NO: 8), OP1 (SEQ ID NO: 39), OP1 (SEQ ID NO: 9), CBMP-2a (SEQ ID NO: 10), CBMP-2b (SEQ ID NO: 11), CBMP-3 (SEQ ID NO: 12), COP1 (SEQ ID NO: 13), COP3 (SEQ ID NO: 14), COP4 (SEQ ID NO: 15), COP5 (SEQ ID NO: 1), COP7 (SEQ ID NO:2), and COP16 (SEQ ID NO: 16):

Replacement paragraph for the sixth full paragraph on page 65, line 33.

As shown in FIGURE 18, these sequences have considerable homology with the alpha and beta inhibins (SEQ ID NOS: 52, 46, and 47, respectively), three forms of TGF beta (SEQ ID NOS: 48, 49, and 50, respectively), and MIS (SEQ ID NO: 51).

MARKED UP VERSION OF CLAIMS SHOWING AMENDMENTS

46. (Amended) A DNA sequence encoding an amino acid sequence sufficiently duplicative of that of the sequence encoded by the gene of Figure 1A[_] (SEQ ID NO: 40) such that said encoded sequence induces bone or cartilage formation when implanted in a mammal in association with a matrix.

47. (Amended) The DNA of claim 46 encoding the same amino acid sequence as the gene set forth in Figure 1A (SEQ ID NO: 40).

48. (Amended) The DNA sequence of claim 46 encoding:

```
     1        10          20          30          40
OP1        LYVSFR-DLGWQDWIIAPEGYAAYYCEGECAFPLNS
                50          60          70
     YMNATN--H-AIVQTLVHFINPET-VPKPCCAPTQLNA
         80          90          100
     ISVLYFDDSSNVILKKYRNMVVRACGCH (SEQ ID NO: 39).
```

49. (Amended) The DNA sequence of the claim 46 encoding:

```
                                                -5
                                                HQRQA
      1        10          20          30          40
OP1   CKKHELYVSFR-DLGWQDWIIAPEGYAAYYCEGECAFPLNS
                50          60          70
      YMNATN--H-AIVQTLVHFINPET-VPKPCCAPTQLNA
          80          90          100
      ISVLYFDDSSNVILKKYRNMVVRACGCH (SEQ ID NO: 9).
```